IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Steven Z. Wu, et al.		Examiner: Humera N. Sheikh
Serial No.	10/663,568	Art Unit: 1615
Filed:	September 15, 2003	Confirmation No.: 2840
Title:	Microparticle Coated Medical Device	

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APPEAL BRIEF

Sir or Madam:

On August 21, 2009, Applicants appealed to the Board of Patent Appeals and Interferences from the final rejection of claims 25, 28-32, 34 and 35. The following is Applicants' Appeal Brief submitted pursuant to 37 C.F.R. § 41.37.

I. REAL PARTY IN INTEREST

The real party in interest is Advanced Cardiovascular Systems Inc., a California corporation, having a place of business at 3200 Lakeside Drive, Santa Clara, California 95054. The assignment was recorded in the United States Patent and Trademark Office for the parent application, 09/851877, now US Patent No. 6,656,506, on May 9, 2001, in Reel 011800, Frame 0894. Effective February 13, 2007, Advanced Cardiovascular Systems Inc. changed its name to Abbott Cardiovascular Systems Inc.

II. RELATED APPEALS AND INTERFERENCES

Applicants, applicants' assignee, and their counsel are not aware of any related appeals or interferences which would affect, be affected by, or have a bearing on the instant appeal.

III. STATUS OF CLAIMS

Claims 25, 28-32, 34 and 35 have been rejected by the Examiner; the rejections thereof are being appealed herewith. Claims 1-24, 26, 27, and 33 are canceled. Claims 36 and 37 are withdrawn.

IV. STATUS OF AMENDMENTS

All amendments have been entered by the Examiner.

V. SUMMARY OF CLAIMED SUBJECT MATTER

Independent claim 25[1] is directed to a drug loaded stent comprising: a) a radially expandable stent body; b) a coating layer disposed on the stent body; and c) polymeric particles containing a therapeutic substance embedded within the coating layer, wherein the coating layer comprises a polymer different than the polymer from which the particles are made, wherein the coating layer is free from any therapeutic substances (see, for example, specification page 3, lines 25-33; page 6, lines 31-34 and Figure 2; page 12, line 29 to page 13, line 24; page 14, line 28 to page 15, line 2; and "Method 3" of page 16).

Claim 32[2] is directed to a medical device comprising an implantable substrate and a coating layer, wherein the coating layer is free from any therapeutic substances but in-

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[1] 25. A drug loaded stent, comprising:

a radially expandable stent body,

a coating layer disposed on the stent body, and

polymeric particles containing a therapeutic substance embedded within the coating layer, wherein the coating layer comprises a polymer different than the polymer from which the particles are made, wherein the coating layer is free from any therapeutic substances.

[2] 32. A medical device, comprising an implantable substrate and a coating layer, wherein the coating layer is free from any therapeutic substances but includes particles of a polymeric material having a therapeutic substance added thereto, wherein the therapeu-

cludes particles of a polymeric material having a therapeutic substance added thereto, wherein the therapeutic substance is completely encased within the polymer particles (*Id*).

Claims 25 and 32 have been duplicated in the footnotes as they form the primary basis for this appeal.

Applicants have identified several advantages of the invention. Having a coating layer that is free from any therapeutic substances is important because it allows for greater control of the release of the loaded microparticles containing the therapeutic substance. The use of microparticles allows for higher drug-loading at a particular target site. In addition, in the past, "drug release rates may also be inadequate since the rate at which the drug is released or delivered to the target site is a function of the chemical and/or biological properties of the polymer in which the drug is embedded." (specification, page 2, lines 25-28).

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Pending claims 25, 28-32, 34 and 35 are patentable over US 5,886,026 under 35 U.S.C. 103(a) in view of US 6,379,379.

VII. ARGUMENTS

Pending claims 25, 28-32, 34 and 35 are patentable over US 5,886,026 under 35 U.S.C. 103(a) in view of US 6,379,379.

Claims 25, 28-32, 34 and 35, which include independent claims 25 and 32, have been rejected under 35 U.S.C. § 103(a) as obvious over Hunter et al. (US 5,866,026) in view of Wang (US 6,379,379). The Examiner has made at least the following errors in the reasoning behind the rejections.

A. No Rational Reason Given

To establish a *prima facie* case of obviousness, the Examiner has an obligation to construe the scope of the prior art, identify the differences between the claims and the prior art, and determine the level of skill in the pertinent art at the time of the invention.

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tic substance is completely encased within the polymer particles.

To fulfill the obligation, the Examiner must (1) provide an explicit, rational reason based on the foregoing why it would be obvious to modify the prior art to arrive at the claimed invention, (2) there must be a reasonable expectation of success, and (3) the prior art references must teach or suggest all the claim limitations.

Claims 25, 32

Claim 25 requires "polymeric particles containing a therapeutic substance embedded within the coating layer, wherein the coating layer comprises a polymer different than the polymer from which the particles are made, wherein the coating layer is free from any therapeutic substances." As the Examiner admits on page 5 of the Final Office Action dated May 22, 2009, "Hunter does not [teach or suggest] that their coating layer is *free from* any therapeutic substances." Independent claim 32 also has a similar limitation.

In order to cure the deficiency of Hunter, the Examiner cites Wang. However, the Examiner fails to give a rational reason as to why one would incorporated an encapsulated drug of Hunter in the multi-layer structure of Wang, and also why there would be an expectation of success without undue experimentation.

The Examiner's reason for combining the particles of Hunter into the multi-layers of Wang is because "[t]he expected result would be an enhanced stent for beneficial treatment of restenosis." This is a conclusory statement, nothing more. "[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." (*KSR International Co. v. Teleflex Inc.*, 550 U.S. 398, 418, (2007)). The Examiner gives no reason as to how the stents of Hunter or Wang would be enhanced. The Examiner has not articulated how removal of the drug from the Hunter layer would enhance Hunter's efficacy.

The Examiner has also failed to articulate how adding the particles of Hunter to the Wang stent would enhance Wang's efficacy, mostly considering Wang teaches that at least one layer having a drug must be used and teaches how to incorporate the drug. Wang teaches that "[s]ince there are many drugs and many polymers, the stent can have

multiple layers of different polymers with the same or different drugs." (Wang, col. 6, lines 24-26).

Misinterpretation of Wang

The Examiner appears to be misinterpreting the disclosure of Wang as to the drug layers. In the Advisory Action mailed August 6, 2009, the Examiner says that "[t]he secondary reference of Wong (sic) amply demonstrates the use of devices, such as stents, that can contain [a] drug as well as be devoid of any drug." (AA, page 2, lines 4-5). Also, the Examiner states that "[t]hese properties (drug release control) would also be permissible given the devices of Wang, since Wang also teaches devices devoid of [an] active agent." (*Id.* at lines 9-10). Further, the Examiner states that "the reference [Wang] is vividly indicative of therapeutic devices which are free of active agent." (*Id.* at line 15). However, these statements are not correct. As indicated in the paragraph above, Wang teaches that at least one layer has a drug in the layer.

Wang discloses specific techniques for incorporating drugs into the materials. A gel-like material may be used to carry the drugs, and that gel-like material may be applied over the coating or directly to the stent as a coating. (Wang, col. 5, lines 47-49). There are two ways to apply drugs to the materials:

> The first way is to mix the drug with the materials, then coat the mixture onto the stent. They can be cast as film or sheet with drug together, then laminate to the core stent. A second way is to coat or laminate polymer with the core stent without the drug. The stent device is made, then sterilized. Due to their gel-like nature, the stent can then be inserted into a drug solution. The drug will be absorbed into/onto the gel. The stent can then be delivered into the body. The drug will then be released. (Wang, col. 5, lines 50-58).

An additional method of incorporating the drugs into the polymer is disclosed as follows:

> Incorporation of drugs and growth factors into a polymer layer can also be performed by several other methods, including the solvent method, melting method, soaking method and spraying method. If both polymer and drug have a cosolvent, a solution case will be an easy way to

> provide the polymer matrix loaded with the drug or growth factor. If the polymer can be melted at low temperature and the drug or growth factor tolerates heating, a melting method can be used to mix the drug or growth factor into the polymer matrix. Also, a polymer-drug solution or suspension solution can be used for coating to provide a layer containing the drug or growth factor. (Wang, col. 6, lines 36-47).

Therefore, Wang does not teach or suggest the limitation that the coating layer is free from any therapeutic substances, and to the contrary, teaches that at least one layer has a drug in the layer and discloses two ways of incorporating the drug.

At a minimum, to create a *prima facie* case of obviousness, the Examiner must show how Hunter in view of Wang teach or suggest each of the limitations of the present claims, something that clearly has not been articulated in the Final Office Action dated May 22, 2009, nor in the Advisory Action dated August 6, 2009.

The combination of Hunter and Wang fails to teach or suggest a medical device where polymeric particles containing a therapeutic substance are embedded within the coating layer, the coating layer comprises a polymer different than the polymer from which the particles are made, and the coating layer is free from any therapeutic substances.

Applicants have identified the problem to solve and a solution to the problem. Having a coating layer that is free from any therapeutic substances is important because it allows for greater control of the release of the loaded microparticles containing the therapeutic substance. The use of microparticles allows for higher drug-loading at a particular target site. In addition, in the past, "drug release rates may also be inadequate since the rate at which the drug is released or delivered to the target site is a function of the chemical and/or biological properties of the polymer in which the drug is embedded." (See specification, page 2, lines 25-28). Hunter and Wang have both utterly failed to recognize any of these problems. In fact, they both emphatically practice the very problem which the present invention aims to cure - - namely, both Hunter and Wang add their drugs to the layers. Even though Wang does have a drug free layer, Wang mandates the use of a drug within at least one of the layers.

Therefore, independent claim 25 and 32 are not obvious over Hunter in view of Wang. For the above reasons, Applicants submit that the rejections of claims 25 and 32 under 35 U.S.C. § 103(a) are in error, and respectfully request that these rejections be reversed.

Dependent Claims 28-31, 34 and 35

Claims 28-31, 34 and 35 depend from independent claims 25 or 32. As discussed above, independent claims 25 and 32 are not obvious over Hunter in view of Wang. Claims 28-31, 34 and 35 are also not obvious over Hunter in view of Wang for the same reasons. Applicants submit that the rejections of claims 28-31, 34 and 35 under 35 U.S.C. § 103(a) are in error, and respectfully request that this rejection be reversed.

B. Improper Obvious To Try Argument

Even if the Examiner's reason for combining Hunter and Wang were rational, there are so many combinations of layers containing polymers and drugs presented by Wang that one of skill in the art would not have an expectation of success without undue experimentation. **The Examiner is essentially making an "Obvious to Try" argument, which is not permissible.**

MPEP § 2145 (X)(B) states that "An 'obvious to try' rationale may support a conclusion that a claim would have been obvious where one skilled in the art is choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success. [A] person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely that product [was] not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103." (*KSR*, 550 U.S. at 421).

In a recent Federal Circuit case, *In re Kubin*, No. 2008-1184 (Fed. Cir. Apr. 3, 2009), the court reaffirmed the *O'Farrell* approach discussed in the *KSR* opinion, and reiterated that obviousness is still a fact-intensive inquiry. The court singled out two specific situations where "obvious to try" may erroneously be equated with obviousness under § 103.

The first pitfall involves finding it obvious to "vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful." (*Kubin*, slip op. at 14 (quoting *In re O'Farrell*, 853 F.2d 894, 902 (Fed. Cir. 1998))). The court further opined that "where a defendant merely throws metaphorical darts at a board filled with combinatorial prior art possibilities, courts should not succumb to hindsight claims of obviousness." (*Id.*).

The second pitfall occurs when obvious to try was "to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it." (*Kubin*, slip op. at 15 (quoting *O'Farrell* at 903)). *KSR* affirmed that § 103 bars patentability unless "the improvement is more than the predictable use of prior art elements according to their established functions." (*KSR*, 550 U.S. at 417). One key focus of the Federal Circuit was that of *O'Farrell's* discussion of "detailed enabling methodology." The court found that the prior art cited against Kubin's disclosed method provided illustrative instructions on how to use a monoclonal antibody specific to the protein for cloning the gene for that protein, thereby leading to a "reasonable expectation of success" in arriving at Kubin's claims. (*Kubin*, slip op. at 15-16 (quoting *O'Farrell*, 853 F.2d at 902.)).

Wang merely teaches that "[s]ince there are many drugs and many polymers, the stent can have multiple layers of different polymers with the same or different drugs." (Wang, col. 6, lines 24-26). This passage, along with the rest of the Wang disclosure demonstrates the first pitfall, where the prior art fails to demonstrate "either no indication of which parameters were critical or no direction as to which of many possible choices is

likely to be successful." Even though Wang does have a drug free layer, Wang mandates the use of a drug within one of the layers.

As to the second pitfall, both Hunter and Wang fail to disclose any "detailed enabling methodology" related to the selection of layers of polymers, with or without drugs. In *Kubin*, the prior art taught a protein of interest, a motivation to isolate the gene coding for that protein, and illustrative instructions to use a monoclonal antibody specific to the protein for cloning the gene. (*Kubin* at 16). Contrary to *Kubin*, no specific variables are identified as critical in Hunter and Wang, and methods for determining which layer has what drug or which layer doesn't have a drug are not disclosed.

There are many drug, polymer, and drug-polymer layer combinations taught by Wang and no direction as to which of the choices are likely to be successful. At least 45 different types of polymers/coatings are given in column 4, lines 7-31. Wang merely gives general guidance at best. Thus, there is no reasonable expectation of success based on the teachings of Wang to modify the particles of Hunter to arrive at independent claims 25 or 32 of the present invention.

Therefore, claim 25 is not obvious over Hunter in view of Wang. Additionally, claims 28-31 depend from claim 25 and are not obvious for the reasons above. Similarly, claim 35 depends from independent claim 32, which is not obvious in view of Hunter and Wang. Accordingly, dependent claim 35 is not obvious over Hunter in view of Wang.

Applicants respectfully request that the rejection of claims 25, 28-32, 34 and 35 be reversed.

VIII. CONCLUSION

For all of the foregoing reasons it is submitted that all of the Examiner's rejections of claims 25, 28-32, 34 and 35 were in error, and reversal of the Examiner's rejections and allowance of the application are respectfully requested.

The Commissioner is hereby authorized to charge Deposit Account No. 07-1850 for any fees due.

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Respectfully submitted,

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Claims Appendix

25. A drug loaded stent, comprising:

a radially expandable stent body,

a coating layer disposed on the stent body, and

polymeric particles containing a therapeutic substance embedded within the coating layer, wherein the coating layer comprises a polymer different than the polymer from which the particles are made, wherein the coating layer is free from any therapeutic substances.

28. The stent of Claim 25, wherein the polymeric particles are made from a hydrogel material.

29. The stent of Claim 25, wherein the particles are 0.5 to 2 microns in size.

30. The stent of Claim 25, wherein the therapeutic substance is for the treatment of restenosis.

31. The stent of Claim 25, wherein the therapeutic substance is a radioactive isotope.

32. A medical device, comprising an implantable substrate and a coating layer, wherein the coating layer is free from any therapeutic substances but includes particles of a polymeric material having a therapeutic substance added thereto, wherein the therapeutic substance is completely encased within the polymer particles.

34. The stent of claim 25, wherein the therapeutic substance is completely encased within the polymeric particles.

35. The medical device of claim 32, wherein the coating layer comprises a polymer different than the polymer from which the particles are made.

Evidence Appendix

None.

Related Proceedings Appendix

None.